

Correlation Between Inflammatory Biomarkers and Psychological Resilience in Patients With Spinal Metastatic Tumors

Jinguo Chen¹, Guoxian Chen^{*1}, Guosong Xu¹, Weiting Lin¹, Yongda Yue¹

¹ Department of Orthopaedics, The First Hospital of Putian City, Putian, Fujian, China

* Correspondence E-mail: xinlizlx1122@163.com

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Abstract: Spinal metastatic tumors (SMT) are often accompanied by severe pain and significant inflammatory responses, which can adversely affect both the physiological and emotional recovery of patients. Psychological resilience is believed to play a key role in how patients cope with both physical and emotional stress associated with this condition. This study aimed to explore the relationship between inflammatory biomarkers and psychological resilience in patients with spinal metastatic tumors. A prospective observational study was conducted involving 128 patients, from whom blood samples were collected to assess inflammatory biomarkers such as IL-6, TNF- α and CRP. Psychological assessments were performed using the CD-RISC, HADS, and PCS scales. The results revealed a negative correlation between inflammatory markers and psychological resilience scores. ELISA and qPCR results demonstrated higher levels of inflammation in the low resilience group, while western blot analysis revealed significantly elevated expression of IL-6 and TNF- α , indicating a chronic inflammatory state associated with emotional distress. These findings suggest that inflammation may affect emotional regulation and psychological adaptability through a physiological-psychological pathway, highlighting the interconnectedness of inflammation and psychological resilience in patients with spinal metastatic tumors.

1. Introduction

The incidence of spinal metastatic tumors (SMT) has increased significantly in recent years, imposing not only substantial physical burdens but also profound psychological challenges¹⁻³. These patients often suffer from severe pain, inflammation, and the general debilitations associated with advanced cancer, which in turn significantly affect their quality of life⁴. SMT, while clinically recognized for causing neurological impairment and pain, can also exacerbate systemic inflammation and create an emotional burden for patients⁵⁻⁸. Understanding how these physical and emotional challenges interact is crucial for developing more comprehensive treatment strategies. Patients with SMT often face a dual burden, the physical pain and functional limitations due to the tumor's location and metastasis, coupled with emotional and psychological distress. Psychological resilience, defined as an individual's ability to bounce back from adversity, is consid-

ered an important factor in determining how well individuals cope with chronic diseases⁹⁻¹¹. It is hypothesized that individuals with higher psychological resilience are better able to manage the physical and emotional stress associated with conditions like metastatic cancer, which can lead to better health outcomes and improved quality of life^{6,12,13}.

Psychological resilience has been shown to be crucial in the recovery process of patients with chronic conditions. It helps individuals to manage stress, cope with the emotional impact of their illness, and maintain a positive outlook despite ongoing physical challenges¹⁰. In cancer patients, including those with spinal metastasis, resilience may also impact how they respond to pain and treatment, and whether they can effectively adjust to the psychological stressors imposed by their illness¹⁴⁻¹⁸. However, despite its significance, the relationship between psychological resilience and inflammatory responses in these patients remains underexplored.

Inflammation is a central feature of cancer progression and metastasis, and it plays a key role in mediating both the physical symptoms and the psychological responses of patients¹⁹⁻²¹. Inflammatory biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and are frequently elevated in patients with cancer and have been associated with poorer prognosis and increased pain perception²²⁻²⁴. These inflammatory markers are part of the complex neuro-endocrine-immune interactions that regulate not only immune responses but also the nervous and hormonal systems, which influence mood, stress, and emotional regulation^{22,25}. Cortisol and norepinephrine, key stress hormones, are also involved in this interaction and may affect how the body responds to pain and psychological stress^{26,27}.

While numerous studies have examined the relationship between inflammation and psychological outcomes in cancer patients, few have systematically integrated psychological resilience measures, such as Connor-Davidson Resilience Scale (CD-RISC) alongside biomarkers of inflammation and stress. Moreover, the exact pathways through which inflammation might impact psychological resilience and emotional regulation in patients with metastatic spinal tumors are not well understood. This study aims to fill the gap by providing a comprehensive analysis of how inflammatory biomarkers, psychological resilience, and emotional health interact in patients with SMT. By combining CD-RISC scores, biological markers, and validated psychological scales Hospital Anxiety and Depression Scale (HADS-D) and Physical Component Summary (PCS), this research seeks to explore the interplay between the physiological effects of inflammation and the psychological factors that influence how patients cope with the disease. This systematic approach will help to identify potential biomarkers for early identification of patients at risk for psychological distress and poor recovery, and could ultimately inform more effective and personalized treatment strategies for patients with SMT.

2. Results

2.1 Relationship between inflammatory markers, psychological resilience, and pain in patients with SMT

The objective of this study was to explore the relationship between inflammatory markers (such as CRP, IL-6, TNF- α) and psychological resilience scores in patients with SMT, and further investigate the link between inflammatory markers and pain levels. This was a prospective, observational, and cross-sectional study conducted with patients diagnosed with primary or metastatic spine tumors, and experiencing tumor-related pain (Visual Analog Scale (VAS) score ≥ 4). A total of 128 patients were enrolled in the study. Of these, 64 were classified as the high resilience group (CD-RISC score ≥ 60) and the other 64 as the low resilience group (CD-RISC score < 60). Demographic information was collected, along with biological samples from patients. Inflammatory biomarkers such as CRP, IL-6, and TNF- α , as well as cortisol and norepinephrine levels, were measured. Additionally, psychological resilience scores and pain assessments were conducted.

The demographic and clinical characteristics of the two groups at baseline are summarized in **Table 1**. It is noteworthy that the proportion of patients with metastatic tumors in the low resilience group (76.6%) was significantly higher than that in the high resilience group (62.5%), with the difference being statistically significant. Psychological and pain assessments revealed substantial differences between the two groups. The psychological resilience, as measured by the CD-RISC-25 score, was significantly higher in the high resilience group, with an average score of 68.3 ± 6.2 , compared to 49.1 ± 8.7 in the low resilience group. Similarly, the depression scores, assessed by the HADS-D, were markedly lower in the high resilience group compared to the low resilience group. Furthermore, pain scores exhibited significant differences between the two groups. The VAS score in the high resilience group was notably lower than that in the low resilience group. In contrast, no significant differences were observed between the two groups in terms of the Eastern Cooperative Oncology Group (ECOG) performance status, indicating that the functional status of both groups was similar at baseline.

Table 1. Baseline characteristics and psychological scores of patients

Variable	Overall (n=128)	High Resilience Group (CD-RISC ≥ 60 , n=64)	Low Resilience Group (CD-RISC < 60 , n=64)	P-value
Demographic Characteristics				
Age (years)	58.2 ± 10.3	56.1 ± 9.8	60.3 ± 10.5	0.021*
Female (n, %)	62 (48.4%)	28 (43.8%)	34 (53.1%)	0.289
Tumor Characteristics				
Metastatic Tumor (n, %)	89 (69.5%)	40 (62.5%)	49 (76.6%)	0.043*
Psychological Scores				
CD-RISC-25 Total Score	58.7 ± 12.4	68.3 ± 6.2	49.1 ± 8.7	$<0.001^{***}$

HADS-D Depression Score	6.2 ± 3.1	4.1 ± 2.3	8.3 ± 2.8	<0.001***
ECOG Performance Status (0-4)	1.8 ± 0.9	1.7 ± 0.8	1.9 ± 0.9	0.18
VAS (0-10)	7.3 ± 1.7	6.1 ± 1.5	8.5 ± 1.3	<0.01**

*Statistical significance: *P < 0.05, **P < 0.01, ***P < 0.001.

Inflammatory markers, including IL-6, TNF- α , cortisol, and norepinephrine, were measured at baseline and correlated with psychological resilience scores, depression scores, and pain levels. The results of these analyses are presented in **Table 2**. IL-6 levels exhibited a significant negative correlation with the CD-RISC-25 score, suggesting that higher IL-6 levels are associated with lower psychological resilience. Similarly, TNF- α levels were inversely correlated with resilience scores, indicating that elevated TNF- α levels are linked to reduced resilience. Cortisol levels also showed a negative correlation with resilience scores, though to a lesser extent. Additionally, norepinephrine levels demonstrated a weaker, but still significant, negative correlation with resilience scores. Depression scores were positively correlated with all the measured inflammatory markers and hormones. Specifically, IL-6 levels were strongly positively correlated with depression scores, as were TNF- α , cortisol, and norepinephrine levels. These findings suggest that higher levels of inflammatory markers are associated with more severe depressive symptoms.

Further analysis revealed significant positive correlations between inflammatory markers and the PCS and Mental Component Summary (MCS) scores of the SF-36 Health Survey. Although the correlation with cortisol and norepinephrine was somewhat weaker, it remained statistically significant. Additionally, pain levels assessed by the VAS were positively correlated with inflammatory marker levels. Both IL-6 and TNF- α showed a positive correlation with pain scores, indicating that higher levels of these inflammatory markers were associated with greater pain intensity. Cortisol levels demonstrated a weak positive correlation with pain scores, while norepinephrine levels exhibited a moderate positive correlation with pain intensity.

This study demonstrates a significant association between inflammation markers and psychological resilience in patients with metastatic spine tumors. Higher levels of pro-inflammatory cytokines such as IL-6 and TNF- α were linked to lower psychological resilience, higher depression, and greater pain severity.

Table 2. Correlations between inflammatory markers and hormones and psychological scores

Psychological Assessment Metrics	IL-6 (pg/ml)	TNF- α (pg/ml)	Cortisol (μ g/dl)	Norepinephrine (pg/ml)
CD-RISC-25 Total Score	-0.42**	-0.38**	-0.35**	-0.29*
HADS-D Depression Score	0.51**	0.46**	0.39**	0.33**
PCS Total Score	0.47**	0.40**	0.36**	0.31**
MCS Total Score	0.45**	0.41**	0.38**	0.30*

*Statistical significance: *P < 0.05, **P < 0.01

2.2 Inflammatory protein expression and NF- κ B pathway activation in SMT patients

We subsequently investigated the expression of inflammation-related proteins in peripheral blood leukocytes from patients with spinal metastatic tumors, analyzing how different levels of psychological resilience correlate with immune-inflammatory status. Specifically, we measured the expression of two key pro-inflammatory cytokines, IL-6 and TNF- α , in the peripheral blood leukocytes of these patients. Based on their psychological resilience, as assessed by the CD-RISC scores, the patients were divided into two groups: the high resilience group (CD-RISC ≥ 60 , n=3) and the low resilience group (CD-RISC ≤ 60 , n=3). Western blot analysis revealed a significant upregulation of IL-6 and TNF- α expression in the low resilience group compared to the high resilience group (**Fig. 1**). The increase in these inflammatory cytokines in the low resilience group suggests that individuals with lower psychological resilience are in a state of persistent and exacerbated inflammatory activation. These findings support the hypothesis that psychological stress and inflammation are interconnected, with chronic emotional stress potentially leading to sustained inflammatory responses. The elevated IL-6 and TNF- α levels observed in these patients may indicate a continuous inflammatory state, which is a known contributing factor to various chronic diseases, including those affecting the spine. This chronic inflammation may further exacerbate pain and contribute to psychological distress in patients with spinal metastatic tumors. The results of this study highlight the potential mechanistic link between psychological stress and immune dysregulation, particularly in the context of cancer-related pain and psychological resilience.

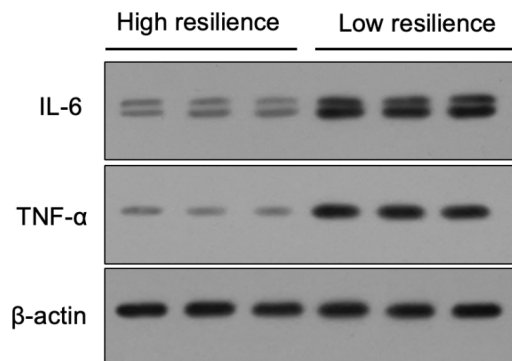


Figure 1. Expression of IL-6 and TNF- α in peripheral blood leukocytes.

In addition to investigating the cytokines IL-6 and TNF- α , we also examined the activation of the NF- κ B signaling pathway in the peripheral blood leukocytes of patients with spinal metastatic tumors. NF- κ B, a crucial transcription factor, plays a central role in regulating immune responses and inflammation^{28,29}. The Western blot analysis revealed a significant elevation in the expression of p65 and a marked reduction in the levels of I κ B α in the low resilience group, in contrast to the high resilience group (**Fig. 2**). Specifically, the low re-

silience group demonstrated markedly enhanced p65 expression and a significant downregulation of I κ B α , which is an inhibitory factor that normally regulates NF- κ B activation³⁰⁻³². These findings clearly indicate that the NF- κ B pathway is substantially activated in individuals with lower psychological resilience. This exaggerated inflammatory state could exacerbate psychological distress and mood disorders, such as anxiety and depression, which are commonly observed in cancer patients. Furthermore, the elevated NF- κ B signaling may exert effects on the central nervous system, perpetuating a vicious cycle wherein psychological stress exacerbates immune activation, which, in turn, worsens both emotional and physical health outcomes. Overall, the activation of the NF- κ B pathway in the low resilience group underscores the potential role of inflammation in mediating both psychological and physiological dysfunction, highlighting the importance of integrating strategies to address both immune and psychological health in the care of cancer patients.

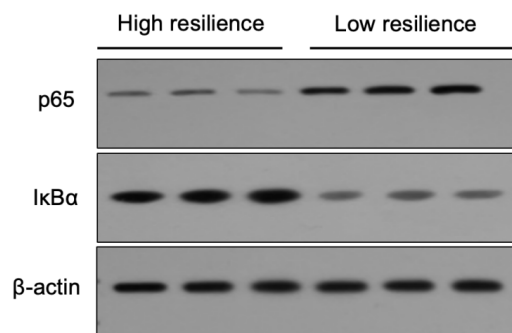


Figure 2. Expression of p65 and I κ B α in peripheral blood leukocytes.

2.3 Impact of psychological resilience on inflammatory biomarkers in SMT patients

The qPCR analysis revealed significant differences in the expression of key inflammatory biomarkers, including IL-6, TNF- α , and CRP, among the control, high resilience, and low resilience groups. **Fig. 3A**, which illustrates IL-6 expression, shows that the low resilience group had significantly higher IL-6 levels compared to both the high resilience and control groups. No significant difference in IL-6 expression was observed between the high resilience and control groups. **Fig. 3B** presents TNF- α expression, where the low resilience group also exhibited significantly higher levels of TNF- α than both the high resilience and control groups. Similarly, no significant difference in TNF- α levels was found between the high resilience and control groups. **Fig. 3C** displays CRP expression, with results indicating that the low resilience group had significantly elevated CRP levels compared to both the high resilience and control groups. The qPCR results provide strong evidence that psychological resilience plays a critical role in modulating inflammation in patients with spinal metastatic tumors. Lower psychological resilience is associated with higher levels of key inflammatory markers, underscoring the potential influence of psychological factors on immune system

activation and chronic inflammation in this patient population.

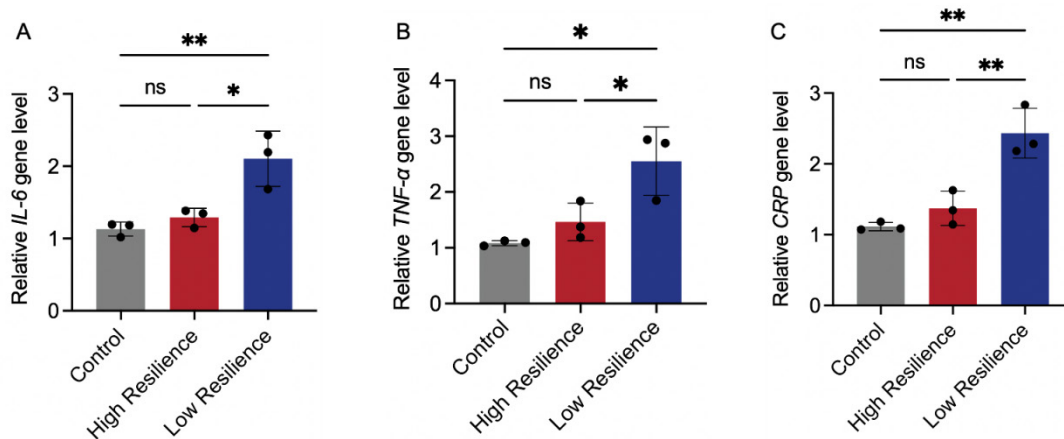


Figure 3. qPCR analysis of peripheral blood inflammatory biomarker levels.

The ELISA results reveal significant differences in the levels of key inflammatory biomarkers IL-10, IL-6, and CRP, across the control, high resilience, and low resilience groups. The low resilience group exhibited significantly higher IL-10 levels compared to both the high resilience and control groups. In contrast, no significant difference in IL-10 expression was observed between the high resilience and control groups (**Fig. 4A**). This suggests that low psychological resilience may be associated with an elevated immune response, characterized by increased anti-inflammatory IL-10 production, which could be compensating for the higher levels of pro-inflammatory cytokines in this group. Furthermore, the low resilience group showed significantly higher IL-6 concentrations compared to both the high resilience and control groups (**Fig. 4B**). As a well-known pro-inflammatory cytokine, IL-6's elevated levels in the low resilience group further support the hypothesis that reduced psychological resilience is linked to a pro-inflammatory state, which may contribute to immune system dysregulation and chronic inflammation. CRP levels were also significantly higher in the low resilience group compared to both the high resilience and control groups (**Fig. 4C**). Elevated CRP levels are a marker of systemic inflammation, reinforcing the notion that lower psychological resilience is associated with heightened inflammatory responses.

Overall, these findings suggest that psychological resilience plays a critical role in modulating systemic inflammation, with lower resilience linked to elevated levels of both pro-inflammatory and anti-inflammatory markers. This imbalance could contribute to immune dysregulation and chronic inflammatory conditions in this patient population.

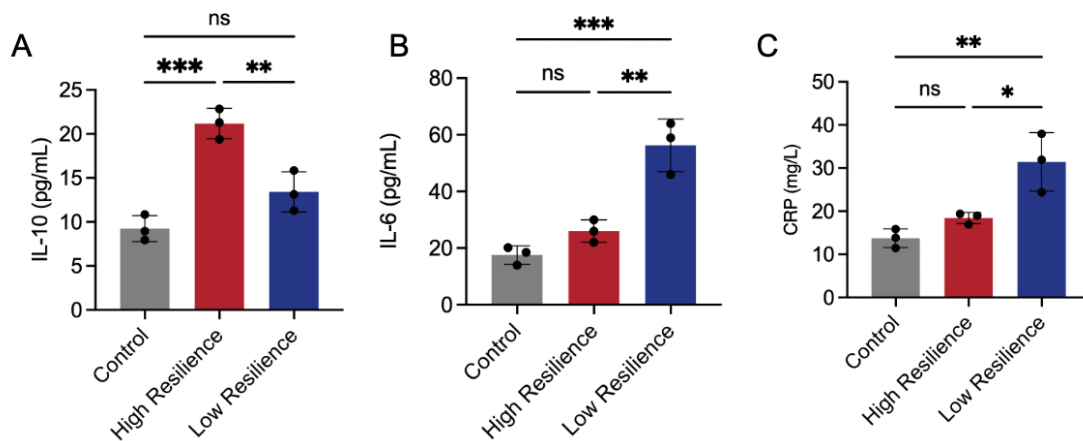


Figure 4. ELISA analysis of peripheral blood inflammatory biomarker levels.

3. Conclusion

This study identifies a clear association between psychological resilience and the inflammatory state in patients with SMT. Our findings demonstrate that lower psychological resilience is closely linked to a more pronounced inflammatory response, as indicated by elevated levels of key inflammatory biomarkers such as IL-6 and TNF- α . Furthermore, we observed a strong correlation between inflammatory markers and psychological stress scores, emphasizing the significant impact of psychological factors on the immune system.

In addition, the anti-inflammatory cytokine IL-10 was identified as potentially having a protective role, suggesting that it could counteract the heightened inflammatory state seen in patients with low resilience. This highlights the importance of considering anti-inflammatory pathways as a potential therapeutic target in managing the inflammatory burden associated with low psychological resilience.

The clinical implications of this study are significant. Inflammatory biomarkers, such as IL-6, TNF- α , and CRP, could serve as useful auxiliary screening indicators for psychological interventions, offering a more comprehensive approach to patient care. Moreover, integrating physiological and psychological assessments into a holistic evaluation of patients with SMT can enhance their overall management, improving both their emotional and physical recovery. This combined approach underscores the need for personalized treatment strategies, which take into account the interplay between immune responses and psychological well-being, thereby contributing to better overall care for spinal tumor patients.

4. Methods

4.1 Clinical Data Collection Method. This study included patients diagnosed with spinal tumors, either primary or metastatic, confirmed by histopatho-

logical examination. To be eligible for participation, patients needed to meet the following inclusion criteria: the presence of tumor-related low back pain with a Visual Analog Scale (VAS) score of 4 or higher, age between 18 and 75 years, the ability to participate in psychological resilience assessments and inflammatory marker evaluations, and voluntary participation with signed informed consent. Patients were excluded if they had severe psychiatric disorders (such as depression or anxiety), acute inflammatory or autoimmune diseases, other malignancies or systemic diseases, or if they were unable to comply with the experimental protocol.

Demographic information was recorded, and various inflammatory biomarkers including CRP, IL-6, and TNF- α , as well as cortisol and norepinephrine levels, were measured. In addition, psychological resilience was assessed using standardized questionnaires such as the Connor-Davidson Resilience Scale (CD-RISC), and pain levels were evaluated using the VAS.

4.2 Western blot analysis. Peripheral blood (10-20 mL) was collected from patients using standard venipuncture methods. Peripheral blood leukocytes (PBLs) were isolated through density gradient centrifugation, typically using the Ficoll-Paque method. The leukocyte pellet was resuspended in RIPA lysis buffer containing protease and phosphatase inhibitors and incubated on ice for 30 mins, with occasional vortexing to ensure complete cell lysis. After centrifugation at 12,000 g for 15 mins at 4°C to remove cellular debris, the supernatant was transferred to a clean tube for protein quantification. The total protein concentration was measured using a BCA protein assay kit.

For SDS-PAGE and Western blotting, 12-15% SDS-PAGE gels were prepared for protein separation. Equal amounts of protein (20-40 μ g) from each sample were loaded into the gel, and electrophoresis was performed at 120V for 1-2 h, depending on the gel size. The proteins were then transferred to a PVDF membrane at 100V for 1 h. The membrane was blocked with 5% non-fat milk in TBST (Tris-buffered saline with 0.1% Tween-20) for 1 h at room temperature to prevent non-specific binding. Primary antibodies, IL-6 antibody (Btyotim, AF0201), TNF- α antibody (Btyotim, AF8208), I κ B α antibody (Btyotim, AI096) and NF- κ B P65 antibody (Btyotim, AN365) were applied and incubated overnight at 4°C with gentle shaking. After washing with TBST, the membrane was incubated with the appropriate HRP-conjugated secondary antibody for 1 h at room temperature.

Following additional TBST washes to remove excess secondary antibody, protein detection was carried out using a chemiluminescence substrate, such as ECL. Protein bands were visualized using a Western blot imaging system. The intensity of the protein bands was quantified using image analysis software, such as ImageJ or Bio-Rad's Image Lab, and results were normalized to internal loading controls, such as β -actin or GAPDH, for accurate comparisons.

4.3 qPCR. For the analysis of inflammatory biomarkers in patients with SMT, peripheral blood samples were collected from each patient using standard

venipuncture methods. The collected blood (10-20 mL) was processed to isolate peripheral blood mononuclear cells (PBMCs) by density gradient centrifugation using Ficoll-Paque. The PBMCs were then resuspended in an appropriate lysis buffer for RNA extraction.

Total RNA was extracted from the isolated PBMCs using a commercial RNA isolation kit (e.g., TRIzol reagent or similar) following the manufacturer's instructions. RNA concentration and quality were assessed using a NanoDrop spectrophotometer or a similar device. After confirming the integrity of the RNA, cDNA was synthesized from 1 µg of total RNA using a reverse transcription kit (e.g., SuperScript III or similar), according to the manufacturer's protocol.

qPCR was performed using specific primers for the target inflammatory biomarkers, including IL-6, TNF- α , and CRP. The qPCR reaction was carried out using a SYBR Green-based master mix (or a probe-based system, depending on the assay) on a real-time PCR machine. The thermal cycling conditions were as follows: initial denaturation at 95°C for 10 mins, followed by 40 cycles of denaturation at 95°C for 15 s, annealing at the optimal temperature for each primer (typically 55-60°C) for 30 s, and extension at 72°C for 30 s.

The relative expression levels of each target gene were calculated using the $\Delta\Delta C_t$ method, with normalization to the housekeeping gene. The results were expressed as fold changes in gene expression between different patient groups or compared to control groups. Statistical analysis, including appropriate tests (ANOVA), was performed to determine significant differences in gene expression levels across groups. Primer sequences used are as follows:

IL-6 (F: ACAGCCAGAGTCCTTCAGAG, R: CCAGGTAGCTATGAGGAGTG); TNF- α (F: GAGGCCCATAGAACTGATGG, R: GTTGAGGGTCTGGGCCATAG); CRP (F: CGGCAGCAGGAAAGAGTTGA, R: GGGA-CAGGCTGTACAGTGA).

4.4 ELISA. For the assessment of inflammatory biomarkers in patients with SMT, peripheral blood samples were collected from each patient using standard venipuncture methods. A total of 10-20 mL of blood was drawn and processed to isolate plasma or serum using standard centrifugation techniques at 3000 g for 10 mins at 4°C. The supernatant was carefully separated and stored at -80°C until further analysis. After washing the plate, patient plasma or serum samples were added to the wells and incubated for 2 hs at room temperature.

Following the incubation, the plate was washed again to remove any unbound sample. The appropriate detection antibody, which is conjugated with an enzyme (HRP), was added and incubated for 1 h at room temperature. After another round of washing, the substrate solution (TMB substrate) was added to the wells, and the plate was incubated for 10-15 mins, or until a visible color change occurred.

The reaction was stopped using a stop solution, and the absorbance was measured at the appropriate wavelength (450 nm) using a microplate reader. The concentration of each inflammatory biomarker in the plasma or serum samples

was determined by comparing the absorbance values to a standard curve generated from known concentrations of the biomarker.

4.5 Statistical Analysis. All experiments were performed in triplicate, and data are presented as mean $\pm$ SEM. Statistical analysis was performed using GraphPad Prism software. Data were analyzed using the t-test for comparisons between two groups and ANOVA for comparisons among multiple groups. Specifically, the t-test was used for comparing differences between the high and low resilience groups, while ANOVA was applied to analyze differences across more than two groups or time points. Statistical significance was defined as * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

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